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Original Research Article

Buprenorphine Maintenance Subjects Are Hyperalgesic and Have No Antinociceptive Response to a Very High Morphine Dose

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Abstract

Objective. Acute pain management in opioid-dependent persons is complicated because of tolerance and opioid-induced hyperalgesia. Very high doses of morphine are ineffective in overcoming opioid-induced hyperalgesia and providing antinociception to methadone-maintained patients in an experimental setting. Whether the same occurs in buprenorphine-maintained subjects is unknown.

Design. Randomized double-blind placebo-controlled. Subjects were tested on two occasions, at least five days apart, once with intravenous morphine and once with intravenous saline. Subjects were tested at about the time of putative trough plasma buprenorphine concentrations.

Setting. Ambulatory.

Subjects. Twelve buprenorphine-maintained subjects: once daily sublingual dose (range = 2–22 mg); no dose change for 1.5–12 months. Ten healthy controls.

Methods. Intravenous morphine bolus and infusions administered over two hours to achieve two separate pseudo-steady-state plasma concentrations one hour apart. Pain tolerance was assessed by application of nociceptive stimuli (cold pressor [seconds] and electrical stimulation [volts]). Ten blood samples were collected for assay of plasma morphine, buprenorphine, and norbuprenorphine concentrations until three hours after the end of the last infusion; pain tolerance and respiration rate were measured to coincide with blood sampling times.

Results. Cold pressor responses (seconds): baseline: control 34 ± 6 vs buprenorphine 17 ± 2 ($P = 0.009$); morphine infusion-end: control 52 ± 11($P = 0.04$), buprenorphine 17 ± 2 ($P > 0.5$); electrical stimulation responses (volts): baseline: control 65 ± 6 vs buprenorphine 53 ± 5 ($P = 0.13$); infusion-end: control 74 ± 5 ($P = 0.007$), buprenorphine 53 ± 5 ($P > 0.98$). Respiratory rate (breaths per minute): baseline: control 17 vs buprenorphine 14 ($P = 0.03$); infusion-end: control 15 ($P = 0.09$), buprenorphine 12 ($P < 0.01$). Infusion-end plasma morphine concentrations (ng/mL): control 23 ± 1, buprenorphine 136 ± 10.

Conclusions. Buprenorphine subjects, compared with controls, were hyperalgesic (cold pressor test), did not experience antinociception, despite high plasma morphine concentrations, and experienced

respiratory depression. Clinical implications are discussed.

Key Words. **Opioids; Hyperalgesia; Addiction; Pain Medicine**

Introduction

The prevalence of opioid dependence is growing worldwide. Dependence has traditionally been the result of illicit opioid abuse. However, it is increasingly associated with legally prescribed long-term use of opioids for the management of chronic pain [1]. Between 28 and 38.5 million people abuse opioids worldwide. In 2015, 2 million had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin [2]. Approximately 1% of the Australian population is opioid dependent, and half of these are in opioid substitution treatment (OST) programs [3]. Of these, two-thirds receive methadone and one-third buprenorphine (alone or with naloxone), but this difference is declining.

The management of acute pain in opioid-dependent patients is complicated because of two major factors: tolerance, which can generally be overcome by dose increase but may be compromised by adverse effects, and the underrecognized phenomenon of opioid-induced hyperalgesia (OIH), characterized as paradoxical pain sensitization [4], which cannot be overcome by dose increase. Although there are no formal guidelines for the clinician, Macintyre et al. [25] and Huxtable et al. [6] advise that in the clinical setting, the daily OST dose should be maintained and additional opioids used for acute pain management, titrated until satisfactory analgesia is achieved or an adverse effect (e.g., sedation or respiratory depression) occurs. Such an approach requires stringent observation, such as admission to hospital.

Opioid-induced hyperalgesia occurs in opioid (e.g., heroin)-addicted subjects prior to entry into methadone and buprenorphine treatments [7], chronic noncancer pain patients [8], and slow-release morphine-, methadone-, and buprenorphine-maintained subjects [9–12]. Clinically used and very high doses of morphine are ineffective in overcoming OIH and providing antinociception to methadone-maintained patients [11,13] in an experimental setting. Whether the same occurs in buprenorphine-maintained subjects is unknown.

Buprenorphine, a semisynthetic 4,5-epoxymorphinan opioid, shows partial agonist properties for some responses at the mu opioid receptor and variable effects at the kappa and delta receptors [14]. Its major metabolite norbuprenorphine is also active [15], although there is conjecture as to whether it crosses the blood-brain barrier [16]. Opioid agonists such as morphine, over plasma concentration ranges that produce dose-related increases in analgesia, also produce concentration-dependent respiratory depression without any plateau in healthy human volunteers [17]. In contrast, buprenorphine shows dose-dependent increases in analgesia with a limited extent of respiratory depression [17,18]. As a partial agonist, under appropriate conditions, buprenorphine may act as an agonist or antagonist at opioid receptors [19] and has shown antihyperalgesic effects in healthy subjects using a model of intradermal electric stimulation [20]. Therefore, buprenorphine may be unique in its ability to treat acute pain and possibly attenuate OIH.

Previously we showed that methadone-maintained subjects on doses of 2–120 mg per day, under identical experimental conditions that will be described in this study, experienced no antinociception with 55 mg of intravenous morphine but showed a significant reduction in respiratory rate [13]. To date, no studies have examined the effect of different daily buprenorphine doses on the antinociceptive and respiratory responses to morphine.

The aims of the study in buprenorphine-maintained subjects were to: 1) confirm the presence of OIH; 2) ascertain whether very high intravenous morphine doses produce antinociceptive and respiratory depression effects; and 3) determine any relationship between buprenorphine dose and these effects. Our hypothesis is that buprenorphine-maintained subjects are hyperalgesic and that, in contrast to methadone-maintained subjects, they experience antinociception with high morphine doses.

Methods

Ethics

The Research Ethics Committee of the Royal Adelaide Hospital, Adelaide, South Australia, Australia (RAH Protocol no: 010222) and the Institutional Review Board, Friends Research Institute, Los Angeles, California, USA (FRI IRB no: 00-03-057-02) approved the study. Both bodies adhere to the ethical standards set by the Helsinki Declaration (2008). The study was supported by National Institutes of Drug Abuse (NIDA) grant R01 DA 13706-02. This study was not registered on clinicaltrials.gov as it was carried out before the requirement for registration. Subjects provided written informed consent, were paid for their involvement in the study, and were free to withdraw at any time.

Subjects

Twelve pain-free buprenorphine-maintained subjects comprising seven men and five women aged 24 to 42 years (mean = 35 years) were recruited. Their weights ranged between 49 and 97 kg (mean = 71 kg). They had been receiving sublingual buprenorphine (Subutex Reckitt Benckiser, West Ryde, New South Wales, Australia) for 1.5 to 12 months (mean = 4 months) with no dose change. They had been enrolled in a buprenorphine maintenance program for a period ranging between two and 22 months, with a mean of 10 months. The group was stratified according to prescribed and efficacious maintenance dose, with four subjects in each of the dose ranges of 2–8 mg, 9–15 mg, and 16–22 mg per day. Subjects were recruited if they self-reported intravenous heroin use at least once in the previous month. It was considered more ethical to administer morphine to individuals who continued to use illicit heroin, rather than to those who used no opioids, apart from their prescribed buprenorphine. Ten healthy control subjects (five men and five women, aged 21–41 years, mean = 31 years, weight = 59–102 kg, mean = 80 kg) were selected. These subjects were not taking any prescribed medications. They have been described previously [13].

Exclusion Criteria

Exclusion criteria for all subjects included pregnancy or lactation, use of antiretroviral drugs, significant medical or psychiatric illness that required ongoing treatment (except opioid addiction for buprenorphine subjects), daily alcohol consumption exceeding 40 g for men and 20 g for women, severe liver impairment (serum aspartate aminotransferase and alanine aminotransferase concentrations greater than three times the upper limit of normal range and albumin concentrations less than 33 grams per liter) or hemoglobin counts outside the normal range. Healthy control subjects were excluded if they had any personal or family history of addictive behaviors.

Study Design

The study utilized a double-blind placebo-controlled design with four groups of subjects (healthy controls, once daily buprenorphine dose of 2–8, 9–15, and 16–22 mg). Subjects were tested on two occasions, at least five days apart, once with morphine and once with saline. The order of administration was randomized. Buprenorphine subjects were tested at about the time of putative trough plasma concentrations of buprenorphine (approximately 20 hours after the previous buprenorphine dose).

Procedure

Subjects were asked not to use any analgesics or illicit substances for twenty-four hours prior to testing. A urine sample was collected on each study day for the detection of opioids, benzodiazepines, sympathomimetic amines, cannabinoids, and barbiturates. Analysis of these samples confirmed that control subjects had not taken any of these psychoactive substances. Subjects were excluded from the study if they presented on study or screening days showing any signs of intoxication from any substance.

Testing was conducted under constant ambient temperature (24°C) and constant illumination (70 lux). Each session commenced at approximately 8 AM and lasted eight hours. Two in-dwelling catheters (Insyte Autoguard, Becton Dickenson, Sandy, UT, USA) were inserted into peripheral veins on opposite arms. The catheter in the dominant arm served for drug infusion, the catheter in the nondominant arm for blood sampling. On each testing day, saline was infused at 2 mL/min for 30 minutes prior to morphine or saline administration for familiarization.

Morphine Administration

Morphine sulphate (David Bull Laboratories, Melbourne, Australia) infusions of 1 mg/mL were administered intravenously in two 60-minute stages to achieve two consecutive target pseudo-steady-state plasma concentrations [11] using a syringe driver infusion pump (3100 Graseby Syringe Pump, Watford, Hertfordshire, UK). Buprenorphine subjects received an initial bolus of 15.2 mg of morphine sulphate followed by a constant infusion of 8.3 mg/h for one hour to achieve a target pseudo-steady-state plasma concentration of 80 ng/mL (morphine 1). They were then administered an additional bolus of 15.2 mg of morphine sulphate followed by a constant infusion of 16.5 mg/h for one hour to achieve the second target pseudo-steady-state plasma concentration of 180 ng/mL (morphine 2). The prescribed buprenorphine dose was administered one hour after infusions ceased. Control subjects were administered an initial bolus of 2.2 mg morphine sulphate followed by a constant infusion of 1.2 mg/h for one hour to achieve a target pseudo-steady-state plasma concentration of 11 ng/mL (morphine 1). They were then administered 4.95 mg of morphine sulphate followed by a constant infusion of 3.6 mg/h to achieve the second target pseudo-steady-state plasma concentration of 33 ng/mL (morphine 2) [11].

Blood Sampling and Assessment Times

Seven-milliliter blood samples were taken at the following times: prior to the 30-minute saline familiarization infusion, 10 minutes prior to end of this infusion (designated as baseline), and 10 minutes prior to the end of each of the two morphine or placebo saline infusions. Further blood samples were taken at 0.25, 0.5, 0.75, 1.0, 2.0, and 3 hours after the end of the last infusion. The blood samples were centrifuged immediately and the plasma stored at –20°C until assay. Respiration rate was measured and nociceptive tests (see below) were administered immediately after the collection of each blood sample, except at 0.25, 0.50, and 0.75 hours after the last infusion.

Nociceptive Tests, Physiological Responses, and Safety Monitoring

Two nociceptive tests were administered: the cold pressor using the nondominant arm and electrical stimulation using the earlobe. These tests have been described previously [10]. Cold pressor involves the immersion of the nondominant arm in 0.5°C–1.5°C water, and the response metric is seconds. Electrical stimulation involves the transmission of an electrical pulse through the earlobe and is measured in volts. One nociceptive marker was used, which was pain tolerance, when the participant verbally indicated that they could no longer tolerate the pain and removed their arm from the water or requested that the electrical stimulation cease.

Respiration rate was measured over one minute by observation without the subjects' awareness. Safety was monitored and recorded throughout the study by means of continuous pulse oximetry, continuous electrocardiogram waveform, categorical nausea scale [21], and categorical sedation scale [22].

Plasma Opioid Quantification

The quantification of plasma buprenorphine and norbuprenorphine was by high-performance liquid chromatography coupled to mass spectrometry, as previously described [23]. The assay had a limit of quantification of 0.125 ng/mL for both analytes and all variability in accuracies, and precision had coefficients of variation for buprenorphine and nor-buprenorphine of less than 15%. The quantification of plasma morphine was by high-performance liquid chromatography (HPLC) with coulometric detection, as previously described [11]. The assay had a lower limit of quantification of 1 ng/mL, and all variability in accuracies and precision had coefficients of variation below 7%.

Data Analysis

Data are presented as mean ± SEM (with 95% confidence intervals [CIs]). One-way analysis of variance (ANOVA) was used to compare each outcome variable across treatments for the buprenorphine combined subjects and the control subjects with 95% CI of differences. Unpaired samples *t* tests were used to compare baseline values between the combined buprenorphine subjects and the control subjects. The Pearson product-moment correlation coefficient (Pearson's *r*) was used to measure the linear correlation between individual buprenorphine daily doses and plasma morphine concentrations. Bonferroni's and Dunnet's tests were used for post hoc analyses as appropriate. Data for both studies were analyzed using GraphPad Prism 4.2 for Windows (GraphPad Software, San Diego, CA, USA), and $P < 0.05$ was considered significant.

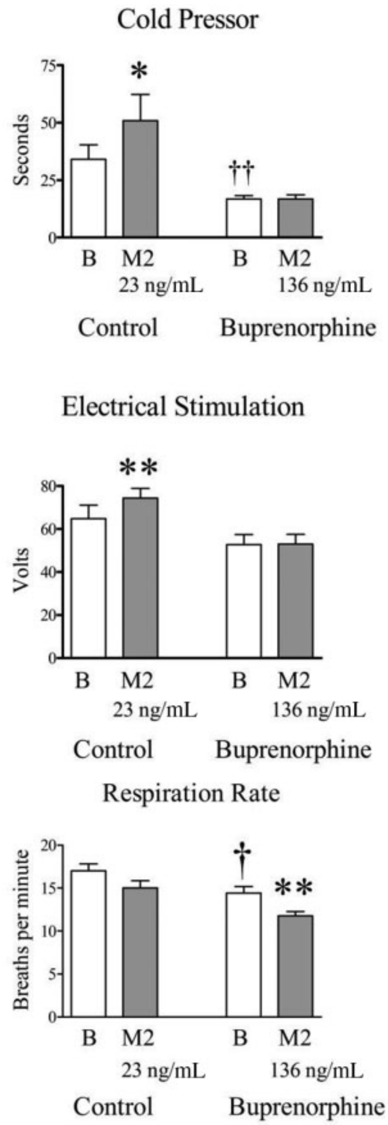

Figure 1 Cold pressor pain tolerance responses (upper panel), electrical stimulation pain tolerance responses (middle panel), and respiration rate (lower panel) mean (±SEM) pain in 10 healthy control and 12 buprenorphine subjects at baseline (B) and morphine infusion 2 (M2). The morphine concentrations between buprenorphine and control subjects were different. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ between groups; $^{*}P < 0.05$, $^{**}P < 0.01$ between treatments.

Results

Nociceptive Tests

There were no significant differences ($P > 0.45$) in pain tolerance responses between the three buprenorphine dose groups from baseline to morphine infusion 1 or morphine infusion 2. Hence, the data from the groups were combined.

Cold Pressor Responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects and the buprenorphine subjects are shown in Figure 1 (upper panel), and absolute values and ranges for all treatments in Table 1. Pain tolerance values for the buprenorphine subjects remained

Table 1 Cold pressor and electrical stimulation responses and respiration rates for 12 buprenorphine-maintained and 10 control subjects on morphine administration days

Response	Group	Baseline	Morphine 1†	Morphine 2‡
Cold pressor, seconds	Control	34 ± 6** (4–73)	38 ± 7 (5–64)	52 ± 11*** (7–23)
	Combined buprenorphine§	17 ± 2 (9–18)	17 ± 2 (4–29)	17 ± 2 (4–27)
Electrical stimulation, volts	Control	65 ± 6 (38–100)	68 ± 5 (48–100)	74 ± 5**** (60–100)
	Combined buprenorphine§	53 ± 5 (24–92)	53 ± 4 (24–72)	53 ± 5 (34–96)
Respiration rate, breaths per minute	Control	17 (14–22)	16.5 (13–19)	15 (10–19)
	Combined buprenorphine§	14* (12–20)	12.5 (10–17)	12**** (9–16)
	2–8 mg ($P = 0.024$)‖	15.5 ± 1.6 (13–20)	11.5 ± 0.9*** (10–13)	11.5 ± 1.3*** (9–15)
	9–15 mg ($P = 0.004$)‖	15 ± 1.2 (12–17)	15 ± 1.1 (12–17)	11.5 ± 0.6**** (10–13)
	16–22 mg ($P = 0.016$)‖	14.8 ± 0.5 (14–16)	12.3 ± 0.6*** (11–14)	12.8 ± 1.3*** (10–16)

*$P < 0.05$, **$P < 0.01$ buprenorphine vs control, ***$P < 0.05$, ****$P < 0.01$ morphine 2 vs control.

†For buprenorphine-maintained subjects, morphine 1 was an initial 15.2-mg bolus of morphine sulphate followed by 8.3-mg/h constant infusion for one hour.

‡Morphine 2 was a 15.2-mg bolus of morphine sulphate followed by 16.5-mg constant infusion for one hour. For controls, morphine 1 was an initial bolus of 2.2 mg of morphine sulphate followed by 1.2-mg/h constant infusion for one hour. Morphine 2 was a 4.95-mg bolus of morphine sulphate followed by constant infusion of 3.6 mg/h for one hour. Data for the nociceptive responses are mean ± SEM (range), and for respiration rates they are median (range).

§The results for the three buprenorphine dose groups are combined.

‖Analysis of variance P values comparing baseline with morphine 1 and morphine 2.

unchanged between baseline and the two morphine infusions. Pain tolerance values for the buprenorphine subjects were significantly lower than for control subjects at baseline (ANOVA $P = 0.009$, 95% CI = −5 to −30). Within-group comparisons revealed that pain tolerance values for control subjects increased significantly ($P = 0.04$) from baseline to morphine infusion 2 ($P < 0.05$, 95% CI = 2 to 34), but not baseline to morphine infusion 1 ($P > 0.05$, 95% CI = −12 to 20).

Electrical Stimulation Responses

Pain tolerance responses at baseline and morphine infusion 2 for control subjects and the buprenorphine subjects are shown in Figure 1 (middle panel), and absolute values with ranges are given in Table 1. Pain tolerance values for the buprenorphine subjects were not significantly different than controls (ANOVA $P = 0.13$) at baseline. Within-group comparisons revealed that pain tolerance values for control subjects increased significantly ($P = 0.007$) from baseline to morphine infusion 2 ($P < 0.01$, 95% CI = 3 to 16), but not baseline to morphine infusion 1 ($P > 0.05$, 95% CI = −2.8 to 10). There was no significant change ($P = 0.98$) in pain tolerance values for combined buprenorphine subjects from baseline to morphine infusion 1 or morphine infusion 2.

Respiration Rates

Respiration rates (breaths per minute) relative to baseline and morphine infusion 2 are shown in Figure 1 (lower panel), and absolute values with ranges are shown in Table 1. Respiration rates for the buprenorphine subjects were significantly lower than for control subjects at baseline (ANOVA $P = 0.03$, 95% CI = −0.25 to −4.9). Within-group comparisons revealed that the respiration rates for control subjects did not decrease significantly ($P = 0.09$) from baseline to morphine infusion 1 or morphine infusion 2. Respiration rates for the buprenorphine subjects decreased significantly (ANOVA $P = 0.006$) from baseline to morphine infusion 2 ($P < 0.01$, 95% CI = −0.9 to −4.4) but not morphine infusion 1 ($P > 0.05$, 95% CI = −2.8 to 10).

Buprenorphine dose group comparisons demonstrated significant changes in respiration rates as follows: group 2–8 mg daily: (ANOVA $P = 0.024$) from baseline to morphine infusion 1 ($P < 0.05$, 95% CI = −0.56 to −7.4) and baseline to morphine infusion 2 ($P < 0.05$, 95% CI = −0.56 to −7.4); group 9–15 mg daily: (ANOVA $P = 0.004$) between baseline and morphine infusion 2 ($P < 0.01$, 95% CI = −1.48 to −5.52), but not morphine infusion 1 ($P > 0.05$, 95% CI = −2.02 to 2.02); group 16 to 22 mg daily: (ANOVA $P = 0.016$) between both baseline and morphine infusion 1 ($P < 0.05$, 95% CI = −0.72 to −4.28) and baseline and morphine infusion 2 ($P < 0.05$, 95% CI = −0.22 to −3.78). There were no significant differences in respiration rate between the groups at baseline ($P = 0.90$) or morphine infusion 2 ($P = 0.67$). The lowest recorded respiration rates were 10 breaths per minute in the control group and nine breaths per minute in the buprenorphine subjects.

Table 2 Plasma morphine concentrations (ng/mL) on morphine administration days in 12 buprenorphine-maintained and 10 healthy control subjects

	Morphine 1	Morphine 2
Control subjects	7.0 ± 0.4	23 ± 1
All buprenorphine subjects	62 ± 4 (42–87)	136 ± 10 (48–201)
Buprenorphine subjects 2–8 mg/d	70 ± 8 (42–87)	175 ± 15 (119–201)
Buprenorphine subjects 9–15 mg/d	60 ± 4 (48–71)	129 ± 9 (48–108)
Buprenorphine subjects 16–22 mg/d	57 ± 4 (52–71)	109 ± 8 (92–129)

The infusion regimens for buprenorphine-maintained subjects and healthy control subjects on morphine 1 and morphine 2 days are described in the *Methods* section. Data are mean ± SEM (range).

Table 3 Plasma buprenorphine concentrations (ng/mL) at baseline and on morphine administration days in 12 buprenorphine-maintained subjects

	Baseline	Morphine 1	Morphine 2
All buprenorphine subjects	1.2 ± 0.3 (0.23–3.31)	0.95 ± 0.19 (0.16–2.3)	1.03 ± 0.23 (0.19–2.98)
Buprenorphine subjects 2–8 mg/d	0.71 ± 0.23 (0.42–1.17)	0.46 ± 0.12 (0.16–0.76)	0.45 ± 0.10 (0.16–0.57)
Buprenorphine subjects 9–15 mg/d	1.45 ± 0.45 (0.23–3.31)	1.14 ± 0.36 (0.24–2.3)	1.40 ± 0.53 (0.19–2.98)
Buprenorphine subjects 16–22 mg/d	1.17 ± 0.28 (0.8–1.98)	1.23 ± 0.24 (0.79–1.79)	1.33 ± 0.22 (0.79 to1.87)

The morphine infusion regimens on morphine 1 and morphine 2 days are described in the *Methods* section. Data are mean ± SEM (range).

Adverse Events

There were no serious adverse events. Buprenorphine subjects did not experience nausea or vomiting, but seven control subjects required one dose of intramuscular metoclopramide hydrochloride 10 mg (Pfizer, Perth, Australia) with good effect for mild vomiting.

Plasma Morphine, Buprenorphine, and Norbuprenorphine Concentrations

Pseudo-steady-state plasma morphine concentrations for morphine 1 and 2 infusions are shown in Table 2. Target pseudo-steady-state plasma morphine concentrations for the buprenorphine recipients were 80 ng/mL (morphine 1) and 180 ng/mL (morphine 2). Target pseudo-steady-state plasma concentrations for control subjects were 11 ng/mL (morphine 1) and 33 ng/mL (morphine 2). Pseudo-steady-state plasma morphine concentrations were lower than the desired target in both groups at morphine 1 and 2. Plasma morphine concentrations are also shown for the individual daily buprenorphine dose groups 2–8, 9–15, and 16–22 mg/d. There was no significant correlation ($P = 0.08$) between individual buprenorphine doses and plasma morphine concentrations at morphine infusion 1. However, there was a significant inverse relationship between individual buprenorphine doses and plasma morphine concentrations at morphine infusion 2 (Pearson's $r = -0.74$, $P = 0.006$, slope 95% CI = −0.92 to −0.28).

There were no significant differences between combined mean plasma buprenorphine concentrations (Table 3) or for the three dose groups, at baseline ($P = 0.64$), morphine infusion 1 ($P = 0.71$), or morphine infusion 2 ($P = 0.51$). Likewise, there were no significant differences between combined mean plasma norbuprenorphine concentrations (Table 4) or for the three dose groups, at baseline, morphine infusion 1, or morphine infusion 2. At baseline on the saline administration day, plasma buprenorphine and norbuprenorphine concentrations were correlated to the buprenorphine dose ($r^2 = 0.36$ and 0.58, respectively) (Supplementary Data).

Discussion

To our knowledge, this is the first study to have examined the effect of added morphine to buprenorphine OST subjects who were pain-free at the time of study, using an experimental pain model. Buprenorphine subjects were hyperalgesic in the cold pressor test in comparison with controls. Very high doses of morphine (55 mg) produced high plasma concentrations (92 to 201 ng/mL) that failed to provide antinociception in either the electrical stimulation or cold pressor tests, irrespective of maintenance buprenorphine dose. In

Table 4 Plasma norbuprenorphine concentrations (ng/mL) at baseline and on morphine administration days in 12 buprenorphine-maintained subjects

	Baseline	Morphine 1	Morphine 2
All buprenorphine subjects	1.7 ± 0.3 (0.30–3.62)	1.61 ± 0.33 (0.31–3.72)	1.85 ± 0.40 (0.34–3.53)

The morphine infusion regimens on morphine 1 and morphine 2 days are described in the *Methods* section. Data are mean ± SEM (range).

contrast, in control subjects, considerably lower morphine doses (12 mg), achieving much lower concentrations (19 to 32 ng/mL), provided antinociception in both tests.

Our choice of using the cold pressor response to study opioid-induced hyperalgesia has been validated by others. Compton et al. [7] examined hyperalgesia in opioid-dependent subjects and found that these subjects, prior to induction and following stabilization on either methadone or buprenorphine, were similarly hyperalgesic in the cold pressor test and did not exhibit hyperalgesia in the electrical stimulation test. Krishnan et al. [12] compared the detection of hyperalgesia in opioid-substitution subjects maintained either on methadone or buprenorphine and healthy controls using the following pain stimuli: cold pain, electrical stimulation, mechanical pressure, and ischemic pain. They found that cold pain was the most suitable of the methods tested to detect opioid-induced hyperalgesia.

While the buprenorphine-maintained subjects were tolerant to the antinociceptive effects of the high doses of morphine and plasma concentrations to which they were exposed, complete cross-tolerance to the respiratory depressant effects of morphine did not occur. Respiration rates dropped significantly across all dose groups, but by a limited amount (approximately 1.5 breaths per minute), which may not be clinically significant. In healthy volunteer subjects who received a single intravenous dose (0.2 mg/kg) of morphine over a plasma concentration range (approximating 3–13 ng/mL) that produced a systematic increase in analgesia, morphine produced significant respiratory depression [24]. In contrast, in healthy adult volunteers who had experience with opioids but who were not physically dependent on opioids, Walsh et al. [18] demonstrated that respiratory depression increased with single buprenorphine doses over a range of 1 to 4 mg (a decrease of approximately four breaths per minute), but that this dose effect began to plateau at higher doses, with no difference between a 16-mg and 32-mg dose. In the present study, with subjects chronically maintained on buprenorphine, high doses of added morphine had a limited respiratory depressant effect at all buprenorphine doses. It is, however, possible that higher doses of morphine might produce respiratory depression if such doses are needed to achieve antinociception, given that the lowest respiratory rate recorded was nine breaths per minute. Macintyre et al. [25] showed increased sedation score (a surrogate for respiratory depression) in buprenorphine-maintained patients who received higher doses of morphine equivalents following surgery than in this study.

Hyperalgesia is likely to be present, to a lesser or greater degree, in opioid recipients for whatever indication. Noncancer pain patients, maintained on either methadone or slow-release oral morphine for the treatment of that pain, were shown to exhibit hyperalgesia in the cold pressor test [8], similar to that seen in methadone [13] and buprenorphine subjects (this study) in opioid substitution programs. Chakrabarti et al. [26] found that people with a greater reported experience of pain prior to induction onto buprenorphine maintenance required greater daily doses. The present study found that there was no difference in the degree of hyperalgesia experienced at baseline between the three dose ranges. There was also no difference between the three dose ranges in terms of cross-tolerance to the antinociceptive effects of very high-dose morphine.

The most widely used drugs in opioid substitution programs worldwide are methadone and buprenorphine, with the latter gaining increasing prominence. Methadone-maintained subjects were examined under conditions identical [13] to those for the buprenorphine subjects in this study. The cold pressor test at baseline revealed that the combined methadone subjects were similarly hyperalgesic to the combined buprenorphine subjects. Furthermore, both groups were cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations, and both groups experienced similar decreases in respiration rate with the addition of very high plasma morphine concentrations. While buprenorphine has been used increasingly across the world because of its purported limited effect on respiratory depression and greater safety profile than other opioids such as morphine and methadone [17,27,28], our findings suggest that supplementary opioids for the management of pain in subjects in opioid substitution programs should be added cautiously under adequate supervision to avoid clinically significant respiratory depression.

Koppert et al. [20], in a mechanical hyperalgesia model, found that acutely buprenorphine had a pronounced antihyperalgesic effect and suggested this may have clinical advantages in the management of chronic pain. In observational studies of chronic pain patients who were switched from high-dose full opioid agonists to sublingual buprenorphine [29,30], the switch resulted in meaningful reduction in pain scores. Buprenorphine was more effective than full opioid agonists. The authors postulated that these findings may have resulted from buprenorphine's antihyperalgesic action [29]. However, Ravn et al. [31], using a multimodal testing technique, could not demonstrate any significant differences between morphine and buprenorphine in the profiles of antihyperalgesia and analgesia in healthy volunteers. The present study shows that buprenorphine, a partial mu opioid receptor agonist and kappa receptor antagonist, when used as a maintenance agent, produces similar respiratory depression and hyperalgesia to methadone (a mu opioid receptor agonist) in opioid-maintained subjects tested under the same experimental conditions [13]. These results suggest that, at the buprenorphine doses to which our subjects were exposed, antihyperalgesia could not be demonstrated with the cold pressor test.

Macintyre et al. [25] examined retrospectively pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine (dose range was similar to that in the present study) and methadone as OST. Outcomes in the two patient groups were similar. The postoperative 24-hour analgesia requirement, provided as patient-controlled analgesia (PCA), was defined as morphine dose equivalents. Buprenorphine-maintained patients required an average of 200 mg; methadone-maintained patients required 221 mg. Pain scores were similar across both groups. Sedation scores of 2 or greater occurred in 22.7% and 24.1% of buprenorphine- and methadone-maintained patients, respectively. This important clinical study was not designed to determine possible mechanisms for the outcomes. Our findings, in an experimental setting in pain-free OST patients, complement the findings of this clinical study: Very large morphine equivalent doses result in insignificant analgesia and the development of respiratory depression, albeit small, given the relatively small (compared with the PCA doses in the clinical study) dose of morphine provided to our subjects. Our findings strongly suggest that hyperalgesia is a likely mechanism for the findings of Macintyre et al. [25], in addition to tolerance. It is pertinent that buprenorphine- and methadone-maintained patients behaved almost identically, suggesting that buprenorphine had no antihyperalgesic properties.

We measured plasma concentrations of morphine, buprenorphine, and norbuprenorphine to more accurately assess the extent of exposure by the subject to these analytes, rather than relying simply on the given doses. While there were no significant differences between plasma buprenorphine concentrations for the three dose groups at baseline, there was considerable variability in the range of concentrations. Hyperalgesia occurred across the whole range of plasma concentrations. The lowest individual plasma buprenorphine concentration was 0.16 ng/mL (in the 2–8 mg/d dose group).

Transdermal buprenorphine patches are increasingly used for the management of chronic pain. In Australia, they are available in various strengths, ranging from 10–40 mg, which deliver 10–40 ug/h and are generally applied once a week, likely for prolonged periods. When 10-ug/h patches were administered to healthy volunteers once a week for three doses, the average plasma concentrations were between 0.155 and 0.172 ng/mL across the three periods [32]; 20-ug/h patches administered to healthy volunteers as a single dose yielded mean maximum plateau plasma concentrations of about 0.25 ng/mL between 48 and 96 hours after application [33]; single applications of 35- and 70-ug/h patches yielded mean maximum plasma concentrations of 0.31 and 0.62 ng/mL, respectively [34]. These values fall within the range of plasma concentrations described in the present study that were associated with hyperalgesia. Thus, it would be reasonable to assume that some patients receiving buprenorphine for the management of chronic pain could be hyperalgesic. Kress [34] reviewed several trials/reports of the efficacy of transdermal buprenorphine (varying doses) in patients with cancer and noncancer pain with a minimum duration of observation of three months. In most of the studies, satisfactory pain relief occurred in at least 50% of subjects, suggesting that hyperalgesia may not be universal in patients suffering from pain, rather than those who receive opioids as substitution treatment.

There are several limitations to this study. The sample size was small and not driven by a formal power calculation. However, we based our population size on the results of Doverty et al. [11], who showed highly significant differences in cold pressor tolerance between 16 healthy controls and 16 methadone maintenance subjects. Despite the smaller sample size in this study, significant differences were seen between buprenorphine recipients and the controls. Plasma buprenorphine concentrations were measured only at the putative peak. However, given the long half-life of buprenorphine and that the subjects would have been at steady state, we considered the sampling regimen justified.

What might be the best strategy to improve pain relief in buprenorphine-maintained patients who experience acute pain, such as following surgery or trauma? Reviews from Huxtable et al. [6] and Schug et al. [5] state that in the clinical setting, for the opioid-maintained population, the opioid dose should be increased until analgesia is achieved or sedation occurs and that the dose of the maintenance opioid should be continued without interruption [25]. The purpose of this study was to provide the evidence for opioid dose escalation that would provide antinociception without respiratory depression in the buprenorphine-maintained population. This study demonstrates that buprenorphine-maintained subjects are hyperalgesic at baseline and that very high morphine doses result in limited respiratory depression, but not antinociception. There is a need to explore alternative strategies for providing acute pain relief in buprenorphine (and methadone)-maintained patients. For example, Huxtable et al. [6] and Schug et al. [5] recommend that an adjuvant analgesic alone, or in combination with morphine, may overcome the limitations of cross-tolerance and side effects to provide pain management in the buprenorphine- and methadone-maintained population.

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Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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